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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,689	11/24/2003	Mario Stevenson	UMY-034RCE	3913

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LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,689	STEVENSON ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,18-21 and 75-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18-21 and 75-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/30/09 has been entered.

Claims 16, 17, and 23-44 were canceled.

Claims 1-15, 18-21, and 75-94 remain pending and are under consideration in this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 14, 15, 18-21, 75-84, and 86-94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) in view of Tuschl et al (US 7056704).

Draper taught ribozymes targeting various conserved sites in HIV RNA such as LTR, nef, vif, tat and rev. See column 4, lines 1-3 and 10-15; and column 9, lines 57-66. Note that some of the vif-targeted ribozymes also target pol. See column 10, lines 43-45. The ribozymes are meant to cleave genomic RNA as well as mRNAs expressed from provirus (see column 4, lines 33-37).

Draper did not teach siRNA.

Tuschl taught siRNAs of 21-24 nucleotides (preferably 21 nucleotides) that are structurally and functionally equivalent to dicer cleavage products of longer dsRNAs. See column 28, lines 15-17. The siRNAs may contain modified nucleotides (column 3, lines 36-44), and mismatches relative to the target sequence are allowed at the termini of the siRNAs (column 28, lines 25-32), for example it is routine to include terminal TT dinucleotides regardless of the target sequence.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNAs of Tuschl for the ribozymes of Draper when targeting HIV RNA for degradation. One would have been motivated to do so because siRNAs are more potent than ribozymes. Tuschl al stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20. One would have had a reasonable expectation of success because the target sites of Draper were selected on the basis of their availability for hybridization. See column 10, lines 13-23, and 52-63.

The "expressed from a vector" limitation of claim 84, 86 and 87 does not affect the structure of the siRNA, and so receives it no patentable weight. Similarly, claims 88-93 are included in this rejection because although they recite structural requirements of a vector (e.g. the vector must encode a plurality of siRNAs), these vector structure requirements are given no patentable weight because the claims are drawn to "a small interfering RNA (siRNA)", and not to a vector. The particulars of the vector are not considered to have any effect on the structure of the claimed siRNA, and so are given no patentable weight.

Claims 12, 13, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) and Tuschl et al (US 7056704) as applied to claims 1-11, 14, 15, 18-21, 75-84, and 86-94 above, and further in view of Svoboda et al (Biochem. Biophys. Res. Comm. 287: 1099-1104, 2001).

The teachings of Draper and Tuschl are summarized above and can be combined to render obvious siRNAs directed to portions of an HIV genome. The references did not explicitly disclose shRNAs.

Svoboda taught that shRNAs, expressed from plasmids, were just as effective as dsRNAs comprising separate strands. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute shRNA for siRNA in the invention of Draper as modified by Tuschl. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function,

such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Finally, the substitution of shRNA for siRNA would have yielded predictable results to one of ordinary skill in the art at the time of the invention, in view of the teachings of Svoboda. Thus the invention as a whole was prima facie obvious.

Note, the statement of the rejection above corrects a typographical error in the previous action that indicated that the rejected claims were 13, 14, and 85, instead of 12, 13, and 85. This was clearly a typographical error in view of the fact that claims 12, 13, and 85 are drawn to shRNAs, as are the teachings of Svoboda.

Response to Arguments

Applicant's arguments filed 3/30/09 have been fully considered, but are not persuasive.

Applicant reiterates arguments set forth previously, alleging that the ribozyme and siRNA arts are non-analogous, and that MPEP 2143(B) does not support such a substitution because the results would have been unpredictable. In support of this position, Applicant argued in the response filed 2/19/08 that ribozymes and siRNAs are structurally and functionally distinct. This is unpersuasive for the reasons of record, i.e.

one would have found motivation for the substitution because Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20. One would have had a reasonable expectation of success because the target sites of Draper were selected on the basis of their availability for hybridization. See column 10, lines 13-23, and 52-63.

The remainder of Applicant's argument is based on the position that one of ordinary skill would not have had a reasonable expectation of success in applying siRNA technology to mediate RNA interference of the viral RNA genome of an RNA virus such as HIV. Applicant asserts that one of ordinary skill understood that, in the early stages of infection, the viral genome is condensed by core proteins that would protect it from siRNA attack. The fact that the genome is actually accessible to such attack is asserted to be surprising and unexpected, and to support a finding of non-obviousness. Applicant relies for support on Bitko and Barik (2001) who speculated that respiratory syncytial virus genomic RNA is resistant to RNAi cleavage due to its tight association with nucleocapsid protein. This is unpersuasive because, contrary to applicant's assertion, RSV is not related to HIV. RSV is a negative strand, nonsegmented virus, whereas HIV is a lentivirus, a positive strand retrovirus. HIV and RSV do not share the same nucleocapsid proteins or genomic structure. The teachings of Barik provide no evidence that one of ordinary skill would have expected condensed HIV genomic RNA to be resistant to siRNA attack. On the other hand, Sarver et al

(Science 247: 1222-1225, 1990) showed that ribozymes directed to HIV gag RNA cleaved "incoming viral RNA" when expressed in cells that were subsequently challenged with HIV-1. See abstract; Fig. 4 on page 247; and paragraph bridging pages 247 and 248, especially page 248, left column, lines 16-21. Based on this evidence, one of ordinary skill in the art would have had reason to believe that HIV genomic RNA was accessible to attack by siRNA.

Applicant also argues that one of ordinary skill would have expected HIV to have evolved defense mechanisms to prevent cellular degradation of genetic material, relying on Tanchou (J. Mol. Biol. 252: 563-571, 1995) for support. Tanchou found that HIV-1 nucleoprotein complexes formed in vitro protect a portion of the HIV genomic RNA against degradation by RNase T_1. This is unpersuasive because the evidence of Tanchou does not show that the entire HIV genome was stable against RNase T_1, just the 5' and 3' ends (see abstract), and because Sarver (1990) had already demonstrated that condensed HIV RNA was accessible to nucleolytic attack.

Finally, it must be noted that even if one of ordinary skill in the art at the time of the invention would have believed that siRNAs could not successfully attack HIV genomic RNA at an early stage of infection, i.e. while condensed by core proteins, the claims would still be unpatentable over the cited art. The combined references would result in siRNAs that would promote the degradation of HIV mRNAs and genomic RNAs that are transcribed from a provirus, i.e. RNAs that are condensed by nucleoproteins. This is supported by the evidence of record, i.e. Park (2001) who showed that dsRNAs mediated the degradation of HIV transcripts generated from a DNA template. Applicant

has not pointed to any structural feature of these obvious siRNAs that would distinguish them from the claimed siRNAs, i.e. siRNAs that promote the degradation of condensed genomic viral HIV RNA during an early viral replication cycle event. This is because there is no structural distinction. Absent evidence to the contrary, any siRNA directed to a proviral mRNA, or to genomic RNA generated from the provirus, will also act on the condensed viral genome at an early stage. Even if this were a surprising and unexpected feature, it would not render the claims non-obvious because it is an inherent characteristic of each an every one of the siRNAs that can target an mRNA or viral genome that is generated from the provirus. Something that is old does not become patentable upon the discovery of a new property, and there is no requirement that a person of ordinary skill in the art would have recognized this inherent feature at the time of the invention MPEP 21112(I-II). Even if it was not expected at the time of the invention that the siRNAs produced from the combined references would have acted on condensed genomic HIV RNA, the claimed invention would still have been obvious because the rejection is not predicated on that particular activity. The rejection was predicated on what was known at the time the cited references were published (see MPEP 2141.02 (V)). Because the siRNAs rendered obvious by the prior art are, absent evidence to the contrary, structurally identical to those which can successfully attack the viral genome at an early stage, and the allegedly unexpected characteristic is an inherent feature that was not relied upon in any way to formulate the rejection, the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Richard Schnizer/
Primary Examiner, Art Unit 1635